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Interleukin-1 receptor antagonist (anakinra) for Schnitzler syndrom

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Abbreviations: Interleukin (IL), C-reactive protein (CRP), Immunoglobulin (Ig), ANAs-antinuclear antibodies, AMAs-antimitochondrial antibodies, PET-CT-Positron emission tomography–computed tomography.

Abstract
Schnitzler syndrome is a rare autoinflammatory disease, which is defined by the presence of two major criteria: chronic urticaria and monoclonal IgM or IgG gammopathy, in combination with at least two additional minor criteria: recurrent fever, leukocytosis and/or elevated CRP, objective signs of abnormal bone remodeling and a neutrophilic infiltrate in skin biopsy.

We present a 68-year old female patient with a 10 year medical history of chronic urticaria, recurrent fever, severe arthralgia and increased CRP. Over the years multiple diagnostic investigations were performed without conclusive findings, and therapeutic attempts with anti-histamines and several immunosuppressive agents had failed.

The decision to initiate monotherapy with interleukin-1 receptor antagonist was based on immunohistochemical detection of abundance of IL-1β positive cells in the patient's skin biopsy. After starting treatment with anakinra, disappearance of symptoms could be observed within 24 hours. Discontinuation of the treatment resulted in a rapid relapse of the symptoms. . Finally, already after the initiation of therapy with anakinra, the suspected diagnosis of Schnitzler syndrome could be confirmed by detection of IgM-gammopathy that was initially absent.

Introduction

Schnitzler syndrome is a rare autoinflammatory disease, which according to Strasbourg diagnostic criteria is defined as a combination of chronic urticaria and monoclonal IgM or IgG gammopathy (major criteria) as well as at least two additional criteria: recurrent fever, leukocytosis and/or elevated CRP, objective signs of abnormal bone remodeling and a neutrophilic infiltrate in skin biopsy (minor criteria). Other symptoms

charectaristic for systemic inflammation such as arthralgia, lymphadenopathy and hepato-and/or splenomegaly are often present. (1, 2)

Case report

A 68-year old female patient presented to our department with chronic urticaria resistant to treatment with anti-histamines and classical immunosuppressive agents combined with intermittent fever, severe arthralgia and persistent elevation of CRP. Apart from migraine and hysterectomy the medical history of the patient was otherwise unremarkable.

The patient reported that the urticarial lesions as well as arthralgia and fever had first appeared at the age of 58. Initially the disseminated urticarial skin lesions persisted up to 24 hours. At first, laboratory investigations were within the normal range. Histopathology of the urticarial lesion showed perivascular lymphatic infiltrates without clues for urticarial vasculitis. A skeletal scintigraphy displayed a significantly increased bone remodeling in axial skeleton and metaphyseal areas while a following bone-marrow-biopsy showed inflammatory alteration. Blood investigations indicated a persistently increased CRP. At the onset of the symptoms arthralgia and urticaria were not conceived to be entities of a syndrome. Arthralgia was successfully treated with prednisone orally for two years and a remission could be observed until a severe relapse of joint pain accompanied by urticarial rash and night sweat occurred 12 years later when she presented to a dermatologist. Meanwhile urticaria had been partly controlled with antihistamines not maintaining a complete remission of the urticarial lesions.

Physical examination showed disseminated urticarial lesions (Figure 1A) as well as inguinal and axillary lymphadenopathy. Laboratory investigations showed mild iron deficiency anaemia, persistent elevation of CRP (around 100 mg/l (reference range :<5.0

mg/l)) and a leukocytosis (11.28 x 10^3white blood cells/µl (reference range: 3.0-9.6 x10^3/µl)) with neutrophilia (9.31 x10^3-neutrophils/µl (reference range: 1.5-8.0 x10^3 neutrophils/µl)). Further laboratory testing for autoimmunity showed increased ANAs (1:160 (reference range: <1:10)) while anti-DNS-antibodies and AMAs were in the normal range. Also in serum protein electrophoresis normal pattern could be observed at that time (IgG=11,9g/l (reference range: 7.0-16.0 g/l); IgA=2,5g/l (reference range: 0.7-4.0 g/l); IgM=1,5g/l (reference range: 0.4-2.8 g/l)). Immunofixation, immunoglobulin kappa chain, immunoglobulin lambda chain and kappa/lambda ratio demonstrated normal range. Subsequent routine laboratory examination including diagnostic testing for infectious diseases (lues, brucellosis, rickettsiosis, amoebiasis, helminthosis and borreliosis and parvovirus B19 infection) was negative.

Abdominal ultrasonography detected no pathological change. Ultrasound examination of lymph nodes showed an increased number of inguinal and axillary lymph nodes but no pathological enlargement. A PET-CT scan showed slightly increased activity in the bone-marrow. Based on a followed bone-marrow biopsy it was rated to be reactive in association with the anaemia.

Histologic examination of an urticarial lesion biopsy revealed a neutrophilic urticarial reaction with negative direct immunofluorescence without clues for urticarial vasculitis.

These findings raised a suspicion for a systemic inflammatory disease that might be the underlying cause for the arthralgia, the recurrent urticaria and the fever. However, conventional therapeutic attempts with methotrexate, anti-TNF agents, colchicine and corticosteroids provided only partial improvement of the symptoms.

Therefore 5 years later a repeated skin biopsy with a subsequent immunohistochemical analysis was carried out. Detection of abundant IL-1β expression in patient's skin biopsy (Figure 1G and H) concluded to the decision to initiate monotherapy with the anti-IL-1

antibody anakinra. Consequently 24 hours after systemic administration of anakinra, all clinical symptoms disappeared (Figure 1B) and the inflammatory blood parameters rapidly decreased within the first weeks of the therapy (Figure 1C-F). A short discontinuation of anakinra treatment 1 month later resulted in a rapid relapse and therefore was followed by re-initiation of the therapy.

The clinical picture and the excellent clinical response to anakinra strongly suggested the diagnosis of Schnitzler syndrome. Finally, just two months after the initiation of the treatment IgM-gammopathy could be confirmed in the blood. In a 1.5 year follow-up after the initiation of anakinra, the patient was free of symptoms and apart from a mild erythema at the injection site no adverse drug effects were registered. According to small, open-label, non-comparative studies that also demonstrated efficacy of the long-acting IL-1 blockers canakinumab (3) and rilonacept (4), we switched the therapy to canakinumab due to its longer duration of action (injection every 8 weeks whereas daily for anakinra and weekly for rilonacept) and lower incidence of injection-site reactions.

Discussion

Schnitzler syndrome is a rare, often hard to diagnose disease. Apart from Strasbourg criteria (1) other symptoms characteristic for systemic inflammation such as arthralgia, lymphadenopathy and hepatosplenomegaly are often present.

Making the diagnosis of Schnitzler syndrome at an early onset of the disease might be challenging so as initially the major criteria, especially IgM or IgG gammopathy might not be present.

Due to the variable clinical presentation, setting the diagnosis of Schnitzler symptom is not easy and the patients' history of illness sometimes lasts for years until adequate therapy can be started. As in our case the patient had urticaria, arthralgia, recurrent

fever and increased levels of inflammatory blood parameters for more than ten years. However, for a long time she fulfilled only one of the major criteria – chronic urticaria – while IgM gammopathy was not yet detectable. Therefore nor the diagnosis could be set nor a targeted therapy with IL-1 receptor antagonist could be initiated.

Recently several case reports have reported a high efficacy of the interleukin-1 (IL-1) receptor antagonist anakinra for treating this disease (5, 6)

Schnitzler syndrome is considered to be an acquired, late-onset autoinflammatory disease (7). Its pathogenesis is related to excessive interleukin-1 (IL-1) (8, 9) which is further evidenced by the good and rapid clinical response to IL-1 receptor blockade (7, 10, 11). IL-1 is a pro-inflammatory cytokine that is mainly released by cells of the innate immune system. Production, release and activity of IL-1 are regulated in a complex cascade with synthesis of an inactive precursor protein and inflammasome and caspase-1 dependent activation. Dysfunction or loss of control in this mechanism might explain abnormal secretion of IL-1 and cause IL-1 mediated diseases like Schnitzler syndrome (12). IL-1β may affect almost every cell type and may underlie a variety of different symptoms, such as fever, arthralgia, skin rash or elevated levels of inflammation parameters (13). Upon *in vitro* stimulation with lipopolysaccharide, blood cells from patients with Schnitzler syndrome secrete larger amounts of IL-1β as compared to healthy individuals (14). Furthermore, IL-1β can be detected by immunohistochemistry (IHC) in urticarial lesions of patients with Schnitzler syndrome (11). In our case an increased expression of IL-1β in the skin could be detected by IHC.

However, the pathophysiological mechanisms of the systemic inflammation characterised with the monoclonal gammopathy still remains to be declared. It has been suggested that the monoclonal gammopathy is most likely caused by the systemic

inflammation (15). As also previously demonstrated by our patient who developed a gammopathy only at the latter progress of the disease (16).

With this case we would like to highlight the importance of understanding the pathophysiology of the disease and therefore the possibility of the late onset of the gammopathy. Furthermore we speculate that in some cases the lack of gammopathy is evident only at a late stage of the disease and therofore by the presence of multiple sympthoms reffering to systemic inflammation a treatment with IL-1 receptor antagonist could be considered. Response to IL-1 receptor antagonist has previously suggested to be used as a diagnostic criterion for Schnitzler syndrome (7).

The reported association of Schnitzler syndrome with lymphoproliferative diseases in approximately 15% necessitates even more adequate and early treatment initiation as well as a close follow-up as to not overlook a hematologic malignancy, a possible complication of the Schnitzler syndrome (7, 9). Monotherapy with the IL-1 receptor antagonist anakinra is a highly effective therapeutic option for Schnitzler syndrome (7, 10, 11). Other IL-1 inhibiting agents, such as rilonacept and canacinumab have also demonstrated efficacy in short term studies, further studies are needed to evaluate long term efficacy (4).

Figure legend:

Figure 1: Clinical (A) and histological (G and H) manifestation of Schnitzler syndrome before initiation of treatment with the anti-IL1 receptor antagonist anakinra. Clearance of clinical symptoms (B) after initiation of treatment. Course of blood C reactive protein (CRP) (C), IL-6 (D), leukocyte (E) and neutrophil (F) counts during treatment.

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